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Patient-reported outcomes as predictors of remission in early rheumatoid arthritis patients treated with tight control treat-to-target approach

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Abstract Identifying prognostic factors for remission in early rheumatoid arthritis (ERA) patients is of key clinical importance. We studied patient-reported outcomes (PROs) as predictors of remission in a clinical trial. We randomized 99 untreated ERA patients to receive remission-targeted treatment with three disease-modifying antirheumatic drugs and prednisolone for 24 months, and infliximab or placebo for the initial 6 months. At baseline, we measured following PROs: eight Short Form 36 questionnaire (SF-36) dimensions, patient's global assessment [PGA, visual analogue scale (VAS)], Health Assessment Questionnaire (HAQ), and pain VAS. We used multivariable-adjusted regression models to identify PROs that independently predicted modified American College of Rheumatology remission at 2 years. Follow-up data at 2 years were available for 93 patients (92%), and 58 patients (62%) were in remission. At baseline, patients who achieved remission had higher radiological score ($p=0.04$), lower tender joint count ($p=0.001$), lower PGA ($p=0.005$) and physician's global assessment ($p=0.019$), lower HAQ ($p=0.016$), less morning stiffness ($p=0.009$), and significantly higher scores in seven out of eight SF-36 dimensions compared with patients who did not. In multivariable models that included all PROs, remission was associated with SF-36 dimensions higher vitality (odds ratio 2.01; 95% confidence interval 1.19–3.39) and better emotional role functioning (odds ratio 1.64; 95% confidence interval 1.01–2.68). PGA, pain VAS, HAQ, and other SF-36 dimensions were not associated with remission. We conclude that self-reported vitality and better emotional role functioning are among the most important PROs for the prediction of remission in ERA.

Keywords Rheumatoid arthritis · Clinical trial · Health-Related Quality Of Life · Patient reported outcomes · Remission

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Introduction

At the time of rheumatoid arthritis (RA) diagnosis, it is challenging to predict whether a patient will respond well to therapy. Multiple factors, including lower disease activity, shorter duration of symptoms, and lower Health Assessment Questionnaire (HAQ) score, have been recognized as predictors of remission [1].

Numerous studies have also demonstrated that patient-reported outcomes (PROs) of the American College of Rheumatology (ACR) core data set at baseline predict long-term outcomes in early RA patients [2, 3]. In RA, also individual's psychological characteristics, like coping strategies and differences in illness perception, may contribute to health outcomes [4]. Therefore, quality-of-life instruments including psychological dimensions, like the 36-item Short Form Health Survey (SF-36), might be useful in outcome prediction [5]. To our knowledge, only one previous study has examined the role of SF-36 dimensions in predicting outcomes in an early RA cohort [6].

In the current study, we assessed in a clinical trial setting whether 11 PROs measured at baseline (three ACR core data set PROs and eight SF-36 dimensions) could predict remission independently of other relevant clinical variables in intensively treated early RA patients.

Methods

Patients, study flow, and definition of remission

The NEO-RACo (New Finnish Rheumatoid Arthritis Combination treatment strategy) trial was an investigator-initiated, randomized, controlled, double-blind, multicenter trial, which enrolled 99 patients with early, active, and disease-modifying antirheumatic drug-naive RA fulfilling the ACR 1987 classification criteria [7]. All included patients were of working age (18–60 years). They were assessed clinically at weeks 0, 4, 6, 10, 14, 18, 22, 26, at months 8, 10, 12, and thereafter every 3 months.

Physician's assessment included tender and swollen joint counts, and an assessment of disease activity on a visual analogue scale (VAS) of 100 mm. In addition, blood samples for C-reactive protein, erythrocyte sedimentation rate, and rheumatoid factor were drawn. Intensive triple therapy consisting of methotrexate (10 mg/week), sulfasalazine (1 g/day), hydroxychloroquine (35 mg/kg/wk), and low-dose oral prednisolone (7.5 mg/day) was initiated in all patients. If tolerated, methotrexate and sulfasalazine were titrated up to maximum doses of 25 mg/week and 2 g/day. Swollen joints were treated with intra-articular glucocorticoid injections. In addition, the patients were randomized to receive infliximab or placebo infusions at weeks 4, 6, 10, 18, and 26. If remission was not achieved, or medication was not tolerated, the treatment with traditional disease-modifying antirheumatic drugs (DMARDs) had to be changed as instructed in the study protocol. Further, in treatment failure, defined as less than ACR50 improvement at two consecutive visits after week 26 [8], open label use of biologic DMARDs as rescue therapy was accepted.

Throughout the study, the treatment was targeted to a modified ACR remission, defined as no swollen (66 joint count) or tender joints (68 joint count) and presence of 5 out of the 6 following criteria: morning stiffness <15 min, no fatigue, no joint pain, no tender joints, no swelling in joints or tendons, and erythrocyte sedimentation rate <30 mm/h in women and <20 mm/h in men. Further, disease activity was assessed also using the 28-joint Disease Activity Score (DAS28) [9]. Patient selection criteria of the NEO-RACo trial, as well as the treatment protocol and 2-year outcomes, have been described in detail previously [10].

Patient-reported outcomes

The association between following PROs at baseline and modified ACR remission at 24 months was assessed: the eight dimensions of the SF-36: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health, and the three PROs from the ACR core data set: patient's global assessment of disease activity (PGA) on VAS of 100 mm, patient's assessment of pain on VAS of 100 mm, and patient's assessment of physical function with HAQ [2, 5]. The following wording of the PGA was used: "How would you estimate your rheumatoid arthritis disease activity today?".

Statistical analysis

We made comparisons between groups using *t* test, Mann–Whitney test, or Chi-square test. In the case of violation of the assumptions (e.g. non-normality), a bootstrap-type test was used. We estimated odds ratios for remission at 24 months for 1-SD increases in PROs using generalized maximum entropy estimation methodology for discrete choice models. This method avoids strong parametric assumptions, works well with a limited sample size, and performs well when the covariates, such as SF-36 dimensions, are highly correlated. The models were adjusted for the basic demographic factors (age, sex, and randomization group) and poor prognostic factors—rheumatoid factor, joint damage (modified Sharp/van der Heijde score), and objective measures of disease activity (swollen and tender joint counts, erythrocyte sedimentation rate). The normality of variables was evaluated with the Shapiro–Wilk W

test. The data are presented as means with standard deviations or as counts with percentages. STATA 13.1, StataCorp LP (College Station, TX, USA), statistical package was used for the analyses.

Results

Follow-up data at 24 months were available for 93 (92%) of the 99 patients included in the study. The baseline characteristics of patients who reached and did not reach remission at 24 months are shown in Table 1. Fifty-eight patients (62%) were in remission at 24 months. At baseline, patients who achieved remission had lower tender joint count ($p=0.001$), lower patient's ($p=0.005$) and physician's global assessment ($p=0.019$), lower HAQ ($p=0.016$), less early morning stiffness ($p=0.009$), and higher Sharp/van der Heijde score ($p=0.04$) than patients who did not reach remission. The association between remission and SF-36 dimensions was analysed separately for each dimension. All dimensions except mental health ($p=0.12$) were associated with remission at 24 months (Table 2).

Table 2 Baseline 36-item Short Form Health Survey (SF-36) dimensions (scale 0–100) by remission status at 24 months

SF-36 dimension	Remission at 24 months		*p* value
	No	Yes	
Physical functioning	40 (21)	56 (27)	0.005
Physical role	9 (20)	27 (38)	0.01
Bodily pain	28 (17)	39 (18)	0.003
General health	46 (17)	57 (17)	0.003
Vitality	36 (22)	52 (23)	0.002
Social functioning	59 (28)	75 (24)	0.004
Emotional role	38 (45)	63 (44)	0.01
Mental health	68 (18)	74 (17)	0.12
Summary components			
Physical component	28 (7)	34 (10)	0.003
Mental component	46 (11)	51 (12)	0.02

Numbers are reported as mean (SD)

P values are unadjusted

Table 1 Baseline characteristics of the patients by remission status at 24 months

Patient characteristics	Remission at 24 months		
	No ($n=35$)	Yes ($n=58$)	*p* value
Clinical and demographic characteristics at baseline			
Female, *n* (%)	24 (69)	39 (67)	0.89
Age (years), mean (SD)	45 (10)	47 (11)	0.61
BMI (kg/m^2), mean (SD)	26.3 (5.0)	25.8 (3.7)	0.59
Rheumatoid factor present, *n* (%)	26 (74)	43 (74)	0.99
Duration of symptoms (months), median (IQR)	4 (2, 4)	4 (2, 7)	0.35
Randomized to infliximab, *n* (%)	14 (40)	33 (57)	0.11
Measures of disease activity at baseline			
DAS28, mean (SD)	5.7 (1.3)	5.5 (1.1)	0.31
ESR (mm/h), mean (SD)	33 (24)	33 (21)	0.92
CRP (mg/l), mean (SD)	33 (45)	29 (33)	0.56
Swollen joints (66 joints), mean (SD)	16 (7)	15 (6)	0.41
Tender joints (68 joints), mean (SD)	25 (12)	17 (9)	0.001
PGA VAS (mm), mean (SD)	58 (27)	44 (23)	0.005
Pain VAS (mm), mean (SD)	59 (28)	50 (25)	0.13
HAQ, mean (SD)	1.2 (0.6)	0.8 (0.6)	0.02
PhGA VAS (mm), mean (SD)	58 (20)	48 (19)	0.02
Morning stiffness (min), median (IQR)	120 (100, 240)	90 (60, 180)	0.009
Radiography			
Erosion score, mean (SD)	0.6 (1.2)	2.6 (6.5)	0.02
Narrowing score, mean (SD)	0.2 (0.6)	0.4 (1.4)	0.51
Total score, mean (SD)	0.8 (1.6)	2.9 (7.6)	0.04

Radiographs were assessed according to the modified Sharp/van der Heijde method

BMI body mass index, *IQR* interquartile range, *DAS28* 28-joint Disease Activity Score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PGA* patient's global assessment, *VAS* visual analogue scale, *HAQ* Health Assessment Questionnaire, *PhGA* physician's global assessment

Odds ratios (OR) and 95% confidence intervals (95% CI) for remission at 24 months for 1-SD increase in SF-36 dimensions and ACR core data set PROs are shown in Fig. 1. When core data set PROs and SF-36 dimensions were simultaneously included in the multivariate logistic model, only two SF-36 dimensions, vitality (OR 2.01; 95% CI 1.19–3.39) and emotional role functioning (OR 1.64; 95% CI 1.01–2.68), were associated with increased odds of remission.

Discussion

We investigated whether 11 PROs (three ACR core data set PROs and eight SF-36 dimensions) could be used as predictors of remission in early RA in the era of intensive, remission-targeted treatment. In univariable analyses, PGA, HAQ, and nearly all dimensions of SF-36 predicted remission at 24 months. However, when all PROs were simultaneously included in the regression models with other clinically relevant covariates, only two SF-36 dimensions, vitality and emotional role functioning, were associated with future remission.

We found only one longitudinal study focused on predicting remission in early RA using SF-36 dimensions [6]. In the study by da Mota et al., none of the SF-36 dimensions predicted DAS28 remission (DAS28 < 2.6) in a clinical care setting with 40 RA patients. However, only 23% of the patients achieved remission in the study. Therefore, this study could be underpowered to examine SF-36 dimensions as predictors of outcome. Furthermore, the study was an observational cohort study and not a clinical trial, which increases the risk of bias. For these reasons, it is difficult to compare these results directly with ours.

In our study, none of the ACR core data set PROs (HAQ, PGA, and pain VAS) predicted remission at 24 months after adjustment for SF-36 dimensions and other clinical covariates. HAQ has been previously considered to be one of the most important predictors of outcomes in RA [11, 12]. However, baseline HAQ has not been a potent predictor of clinical remission in early RA in the era of modern remission-targeted treatment, a finding confirmed by the present study [6, 13]. Another core data set component, PGA, has been endorsed as a reliable measure of disease activity although it has also been criticized because non-inflammatory factors, such as pain, seem to contribute to the level of PGA [14]. Even though important in clinical care, according to our findings, PGA does not seem to be useful predictor of future remission.

We found that a 1-SD increase in baseline vitality was associated with twofold greater odds of being in remission at 24 months. Vitality can be defined as the presence of energy, well-being, and the absence of fatigue. So far, only a few studies have reported about the benefits of vitality to physical health. In these studies, higher vitality has been a protective factor against coronary heart disease and stroke [15, 16]. In RA studies, the vitality subscale of SF-36 has been previously used as a validated measure of RA fatigue, defined as low vitality [17]. However, the connection between low vitality (fatigue) and disease activity is still being debated as recent reports have demonstrated that fatigue may be mediated mainly through factors like pain, disability, and poor mental health [18].

Our study was the first to demonstrate that emotional role limitations predict remission. Better emotional role functioning and higher vitality may reflect patients' healthier psychological functioning. This may, in turn, improve patients' ability to cope with RA and RA treatments resulting in better outcomes. Other previous studies have also shown that psychosocial interventions, like cognitive behavioural therapy, relieve RA symptoms effectively [19, 20]. Identifying patients suffering from psychological problems could therefore be of key importance when assessing a patient with newly diagnosed

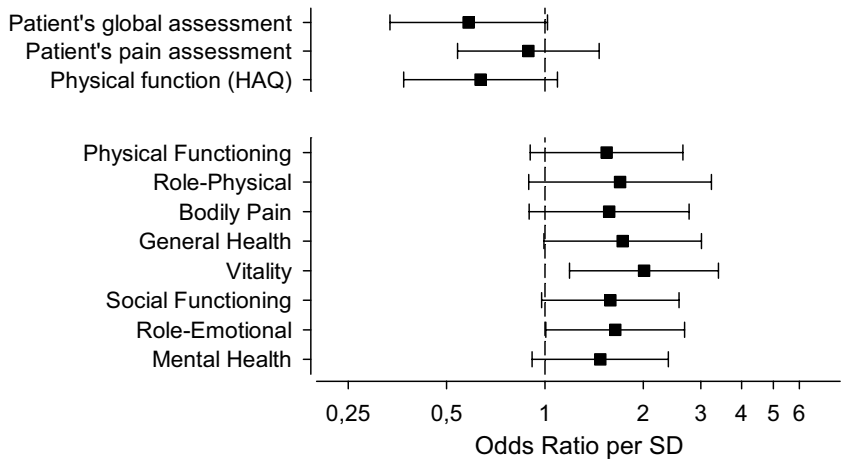

Fig. 1 Odds ratios (OR) and 95% confidence intervals for remission at 24 months for 1 standard deviation (SD) change in baseline ACR core data set PROs and SF-36 dimensions. All variables were simultaneously entered into the model. ORs are adjusted for age, sex, rheumatoid factor status, randomization group, baseline modified Sharp/van der Heijde score, baseline swollen and tender joint counts, and baseline erythrocyte sedimentation rate

RA as these individuals might benefit from psychosocial interventions. Furthermore, it is possible that by measuring vitality and role-emotional functioning, we can grasp aspects of disease activity not detected by simple VAS-based PROs. If future studies confirm the accuracy of vitality and emotional role functioning in predicting remission, questions concerning these SF-36 dimensions could be collected during clinic visits.

The results of our study must be interpreted within the context of their limitations. First, because our study population consisted of intensively treated and followed working age patients with early RA, these results may not be generalizable to other populations and settings. Second, a larger study sample could have resulted in more statistically significant associations although this does not reduce the significance of vitality and emotional role functioning as predictors of remission. Third, SF-36 vitality scale was the only measure of vitality/fatigue used in our study. Because our trial was initiated in 2003, measurement of fatigue in RA clinical trials was not yet widely recommended and therefore other, possibly more comprehensive, fatigue questionnaires were not used. Finally, the prognostic factors of RA are often highly correlated which complicates statistical analysis. However, we tried to minimize the effects of multi-collinearity with the use of generalized maximum entropy estimation methodology.

Our results show that, of the assessed PROs, only vitality and emotional role functioning are associated with higher remission rates in early RA. These self-reported measures may reflect patients' certain personality traits or more positive attitude to life. Further, our results also underline the importance of detecting patients' possible psychological problems and reacting to them. Further studies are needed to elucidate the role and feasibility of these PROs as predictors of remission.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Conflict of interest The authors report following financial activities outside the submitted work: LK has received honoraria and consulting fees from Bristol-Myers Squibb, and Pfizer. KP has received honoraria and consulting fees from Abbvie, Bristol-Myers Squibb, MSD, Pfizer, Roche, and UCB. HK has received honoraria from Abbvie and Pfizer. AK has received honoraria and consulting fees from MSD, Novartis, Roche, and UCB. TM has received an honorary from Pfizer. TY-K has received honoraria and consulting fees from Abbvie, MSD, Pfizer, and UCB. ML-R has received honoraria from Abbvie, Bristol-Myers Squibb, MSD, Pfizer, Regeneron, and Roche. VR has received an honorary from Bristol-Myers Squibb.

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